UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,045	06/30/2006	Alessandro Moretta	INN.133	6062

23557 7590 12/23/2010

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
12/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/563,045	MORETTA ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-79,81 and 83-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *70-79,81 and 83-87* is/are allowed.

6)☒ Claim(s) *88-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Prosecution is hereby reopened in view of Applicant's cancellation of claim 80 and Applicant's argument presented with regard to the 103(a) rejection of record in Applicant's amendment and response filed 12/2/10.

Applicant's amendment and response filed 12/2/10 is acknowledged and has been entered.

2. Applicant' is reminded of Applicant's election without traverse of the Invention of Group I and the species of isolated antibody DF200, a detectable moiety, IL-2 as the additional component, and antibody that binds to KIR2DL1 and KIR2DL2/3 and neutralizes KIR mediated inhibition of NK cell cytotoxicity, in Applicant's amendment filed 4/24/09

Claims 70-79, 81 and 83-91 are presently being examined.

3. Applicant's amendment filed 12/2/10 has overcome the prior rejection of record of claim 80 under 35 U.S.C. 103(a) as being obvious over US 2005/0037002 A1 (of record) in view of Eisenthal *et al* (J. of Immunol. 1990, 144: 4463-4471).

4. Applicant's amendment and response filed 12/2/10 has overcome the prior rejection of record of claims 88-91 under 35 U.S.C. 102(b) as being anticipated by Shin *et al* (Hybridoma, 1999, 18(6): 521-527, abstract). A copy of the full-length Shin *et al* reference is being included with this Office Action.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 88 and 90-91 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim *et al* (J. Immunol. 1997, 159: 3875-3882) as evidenced by Shin *et al* (Hybridoma, 1999, 18(6): 521-527) and by admissions in the specification on page 25 at lines 15-28 and at the paragraph spanning pages 25-26 .

Kim *et al* teach anti-p58 KIR mAbs that interefere with class I-mediated protection of target cells, *i.e.*, they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58 (especially page 3876).

Although Kim *et al* do not *explicitly* teach that the neutralizing anti-p58 mAbs bind to KIR2DL1 and KIR2DL2/3, the evidentiary reference Shin *et al* teach that the mAb that has its epitope in the HLA-binding region in p58 KIR may be the most effective mAb for blocking the interaction between p58 KIR and HLA-C (especially second full paragraph

at line 1, column 1 on page 526), and that HLA-C-recognizing receptor that is inhibitory is the p58 belonging to KIR2DL group comprised of KIR2DL1 and KIR2DL2/3 (especially paragraph spanning pages 521-522). With regard to the limitation recited in instant claim 90, that the mAb competes for binding to KIR2DL1 and/or KIR2DL2.3 on the surface of an NK cell with antibody DF200 produced by the hybridoma deposited as CNCM I-3224, although the art reference does not explicitly teach said ability to compete, the art reference does teach that it interferes with the class I mediated protection of target cells, *i.e.,* that it interferes with the interaction of HLA-C with p58 and neutralizes p58-mediated NK cell cytotoxicity. Like-wise, the antibody DF200 produced by hybridoma CNCM I-3224, possesses this same functional activity (see the recitation in claim 70), while the art reference teaches that a neutralizing antibody recognizes an epitope in the HLA-binding region of p58. Also note that the definition in the specification of "neurtralize KIR-mediated inhibition of NK cell cytotoxicity" may be partial or full neutralization (see below***).

Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the mAb of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

***The admissions in the instant specification on page 25 at lines 15-28 is: "Antibodies of this invention may partially or fully neutralize the KIR-mediated inhibition of NK cell cytotoxicity. The term "neutralize KIR-mediated inhibition of NK cell cytotoxicity," as used herein means the ability to increase to at least about 20%, preferably to at least about 30%, at least about 40%, at least about 50% or more (e.g., about 25-100%) of specific lysis obtained at the same ratio with NK cells or NK cell lines that are not blocked by their KIR, as measured by a classical chromium release test of cytotoxicity, compared with the level of specific lysis obtained without antibody when an NK cell population expressing a given KIR is put in contact with a target cell expressing the cognate MHC class I molecule (recognized by the KIR expressed on NK cell). For example, preferred antibodies of this invention are able to induce the lysis of matched or HLA compatible or autologous target cell populations, i.e., cell populations that would not be effectively lysed by NK cells in the absence of said antibody. Accordingly, the antibodies of this invention may also be defined as facilitating NK cell activity in vivo."

The admissions in the instant specification at the paragraph spanning pages 25-30 is : "Alternatively, the term "neutralize KIR mediated inhibition" means that in a chromium assay using an NK cell clone or transfectant expressing one or several inhibitory KIRs and a target cell expressing only one HLA allele that is recognized by one of the KIRs on the NK cell, the level of cytotoxicity obtained with the antibody should be at least about 20%, preferably at least about 30%, at least about 40%, at least about 50% (e.g., about 25-100%), or more of the cytotoxicity obtained with a known blocking anti MHC class I molecule, such as W6/32 anti MHC class I antibody."

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 88 and 89 are rejected 35 U.S.C. 103(a) as being obvious over Kim *et al* (J. Immunol. 1997, 159: 3875-3882) in view of Harlow and Lane.

Kim *et al* teach anti-p58 KIR mAbs that were found to interefere with class I-mediated protection of target cells, *i.e.,* they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58 (especially page 3876).

Kim *et al* do not teach wherein the antibody is comprised in a composition with a pharmaceutically acceptable excipient.

Harlow and Lane teach that PBS or similar isotonic solutions are commonly used buffers for storing purified antibodies (page 287 at item 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have placed the antibodies taught by Kim *et al* in PBS as taught by Harlow and Lane.

One of ordinary skill in the art would have been motivated to do this in order to store the anti-p58 antibodies.

The skilled artisan was aware that PBS was a storage buffer for antibodies. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

9. Claims 88, 90 and 91 are rejected 35 U.S.C. 103(a) as being obvious over Shin *et al* (Hybridoma, 1999, 18(6): 521-527 in view of Kim *et al* (J. Immunol. 1997, 159: 3875-3882) and by admissions in the specification on page 25 at lines 15-28 and at the paragraph spanning pages 25-26.

Shin *et al* teach that HLA-C-recognizing receptor that is inhibitory is the p58 belonging to KIR2DL group comprised of KIR2DL1 and KIR2DL2/3 (especially paragraph spanning pages 521-522). Shin *et al* teach that the mAb that has its epitope in the HLA-binding region in p58 KIR may be the most effective mAb for blocking the interaction between p58 KIR and HLA-C that it is known that both the γ2 and γ3 domains are involved in the interaction between p58 KIR and its ligand, HLA-C (especially second full paragraph at line 1, column 1 on page 526). Shin *et al* teach the method of mAb production via conventional hybridoma technology of Kohler and Milstein as well as methods for assessing the ability of the mAb to inhibit p58-mediated inhibition of NK cell cytotoxicity (especially materials and methods section).

Shin *et al* do not exemplify wherein the anti-p58 mAb blocks the binding between p58 KIR and HLA-C, nor that it competes for binding with mAb DF200 to KIR2DL1 and/or KIR2DL2/3.

Kim *et al* teach that a polypeptide consisting of the γ2 and γ3 domains can be recombinantly produced, as it folds properly. Kim *et al* teach that their experiments suggest that both Ig domains of p58 are necessary for HLA-C binding and that the binding site on KIR might be the exposed region at the interface between the N- and C-terminal γ domains (see entire reference, especially paragraph spanning columns 1-2 on page 3879). Kim *et al* teach anti-p58 KIR mAbs that were found to interefere with class I-mediated protection of target cells, *i.e.,* they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58 (especially page 3876).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made more mAbs by the conventional hybridoma monoclonal antibody methodology taught by Shin *et al* and to have tested for antibodies that bind to both KIR2DL1 and to KIR2DL2/3 and to have further tested these antibodies for the ability to neutralize KIR-mediated inhibition of NK cell cytotoxicity.

With regard to the limitation recited in instant claim 90, that the mAb competes for binding to KIR2DL1 and/or KIR2DL2.3 on the surface of an NK cell with antibody DF200 produced by the hybridoma deposited as CNCM I-3224, although the art reference does not explicitly teach said ability to compete, the mAb taught by the combined references interferes with the class I mediated protection of target cells, *i.e.,* that it interferes with the interaction of HLA-C with p58 and neutralizes p58-mediated NK cell cytotoxicity. Like-wise, the antibody DF200 produced by hybridoma CNCM I-3224, possesses this same functional activity (see the recitation in claim 70), while the primary art reference teaches that a neutralizing antibody recognizes an epitope in the HLA-binding region of p58. Also note that the definition in the specification of "neurtralize KIR-mediated inhibition of NK cell cytotoxicity" may be partial or full neutralization (see below***).

Therefore the claimed antibody appears to be the similar to the antibody of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the mAb of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the antibody of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

***The admissions in the instant specification on page 25 at lines 15-28 is: "Antibodies of this invention may partially or fully neutralize the KIR-mediated inhibition of NK cell cytotoxicity. The term "neutralize KIR-mediated inhibition of NK cell cytotoxicity," as used herein means the ability to increase to at least about 20%, preferably to at least about 30%, at least about 40%, at least about 50% or more (e.g., about 25-100%) of specific lysis obtained at the same ratio with NK cells or NK cell lines that are not blocked by their KIR, as measured by a classical chromium release test of cytotoxicity, compared with the level of

specific lysis obtained without antibody when an NK cell population expressing a given KIR is put in contact with a target cell expressing the cognate MHC class I molecule (recognized by the KIR expressed on NK cell). For example, preferred antibodies of this invention are able to induce the lysis of matched or HLA compatible or autologous target cell populations, i.e., cell populations that would not be effectively lysed by NK cells in the absence of said antibody. Accordingly, the antibodies of this invention may also be defined as facilitating NK cell activity in vivo."

The admissions in the instant specification at the paragraph spanning pages 25-30 is : "Alternatively, the term "neutralize KIR mediated inhibition" means that in a chromium assay using an NK cell clone or transfectant expressing one or several inhibitory KIRs and a target cell expressing only one HLA allele that is recognized by one of the KIRs on the NK cell, the level of cytotoxicity obtained with the antibody should be at least about 20%, preferably at least about 30%, at least about 40%, at least about 50% (e.g., about 25-100%), or more of the cytotoxicity obtained with a known blocking anti MHC class I molecule, such as W6/32 anti MHC class I antibody."

10. Claims 88-91 are rejected 35 U.S.C. 103(a) as being obvious over Shin *et al* (Hybridoma, 1999, 18(6): 521-527 in view of Kim *et al* (J. Immunol. 1997, 159: 3875-3882) and by admissions in the specification on page 25 at lines 15-28 and at the paragraph spanning pages 25-26, and further in view of Harlow and Lane.

The combination of Shin *et al* in view of Kim *et al* in view of the cited admissions in the specification, has been discussed supra.

The said combination does not teach wherein the antibody is comprised in a composition with a pharmaceutically acceptable excipient.

Harlow and Lane teach that PBS or similar isotonic solutions are commonly used buffers for storing purified antibodies (page 287 at item 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have placed the antibodies taught by Shin *et al* in PBS as taught by Harlow and Lane.

One of ordinary skill in the art would have been motivated to do this in order to store the anti-p58 antibodies.

11. Claims 70-79, 81 and 83-87 are allowed.

12. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644